BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 303 223 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **20.10.93** (51) Int. Cl.5: **A61K 31/545**, C07D 501/46

(21) Application number: **88112910.0**

(22) Date of filing: **09.08.88**

(54) **Water-soluble antibiotic composition and water-soluble salts of new cephem compounds.**

(30) Priority: **10.08.87 GB 8718905**
14.09.87 GB 8721567
26.10.87 GB 8725051
18.12.87 GB 8729574
22.01.88 GB 8801423

(43) Date of publication of application:
15.02.89 Bulletin 89/07

(45) Publication of the grant of the patent:
20.10.93 Bulletin 93/42

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 099 553
FR-A- 2 124 499
FR-A- 2 445 833
US-A- 4 161 527
US-A- 4 241 057

(73) Proprietor: **FUJISAWA PHARMACEUTICAL CO., LTD.**
3, Doshomachi 4-chome
Higashi-ku
Osaka-shi Osaka 541(JP)

(72) Inventor: **Sakane, Kazuo**
15, Azayamagata
Mino
Kawanishi-shi Hyogo 666-01(JP)
Inventor: **Yasuda, Nobuyoshi**
10-12, Kitashowa-cho
Nishinomiya-shi Hyogo 662(JP)
Inventor: **Nishimura, Shintaro**
1-6-30, Gakuen-cho
Settsu-shi Osaka 566(JP)

(74) Representative: **Türk, Gille, Hrabal, Leifert**
Brucknerstrasse 20
D-40593 Düsseldorf (DE)

EP 0 303 223 B1

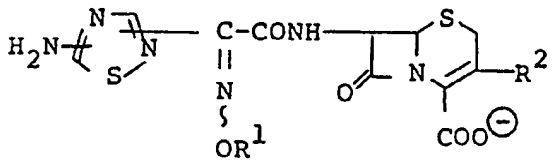
Description

This invention relates to a water-soluble antibiotic composition and salts of new cephem compounds.

More particularly, this invention relates to a water-soluble antibiotic composition which comprises crystals of a cephem compound and a pharmaceutically acceptable carbonic acid salt, and to a process for preparation thereof.

Further, this invention relates to salts of new cephem compounds, to a process for preparation thereof, to a pharmaceutical composition comprising the same and to a use thereof.

In the past, many of the compounds, which are included within the scope of the following chemical formula (II), were prepared, for example, in European Patent Publication Nos. 0027599 and 0188255.



(II)

wherein

R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s), and

R^2 is $(C_1\text{-}C_6)$alkyl substituted with a 5- to 10-membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom, which may have a carbamoyl group on the 5- to 10-membered mono- or bicyclic heterocyclic ring.

The above cephem compounds themselves and their acid addition salts exhibit high antibacterial activity and inhibit the growth of a wide variety of pathogenic bacteria including Gram-positive and Gram-negative bacteria. However, the poor solubility in water of the crystalline compounds and the poor stability of the amorphous solid compounds have prevented their development as injectable medicaments.

Efforts to improve the solubility of insoluble or weakly soluble amphoteric antibiotics have been made by the inventors of FR-A-2 124 499 and FR-A-2 445 833. Further attempts are disclosed in US-A-4 161 527. The results thereof, however, are still unsatisfactory and cannot be applied to each antibiotic compound.

In order to overcome such defects, the inventors of the present invention intensively studied and as a result thereof they have found that the solubility of the crystals of the cephem compound (II) or their acid addition salt, in water was remarkably improved by making the said crystals into a composition with a carbonic acid salt, that is, dissolving the crystals of the cephem compound (II) in water in the presence of a carbonic acid salt.

Further, the inventors continued their study and have found that in an aqueous solution of said compositions, salts of the new cephem compounds derived from the cephem compounds (II) are prepared, which are more highly soluble in water.

Accordingly, the first object of the present invention is to provide a water-soluble antibiotic composition, which comprises crystals of the cephem compounds and a pharmaceutically acceptable carbonic acid salt.

The second object of the present invention is to provide a process for preparation of the above antibiotic composition.

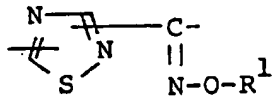
The third object of the present invention is to provide salts of the water-soluble new cephem compounds, which are active against a number of pathogenic microorganisms.

The fourth object of the present invention is to provide a process for preparing the salts of the new cephem compounds.

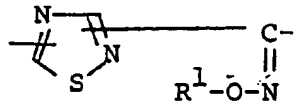
The fifth object of the present invention is to provide a pharmaceutical composition comprising the salts of the new cephem compounds.

And, the sixth object of the present invention is to provide a use of the salts of the new cephem compounds for the manufacture of pharmaceutical composition for treating infectious diseases caused by pathogenic bacteria in human or animals.

With regard to the cephem compound (II) and salts (I) of the new cephem compounds mentioned below, it is to be understood that all of said compounds include syn isomer, anti isomer and a mixture thereof. And, the syn isomer thereof means one geometrical isomer having the group represented by the following formula :



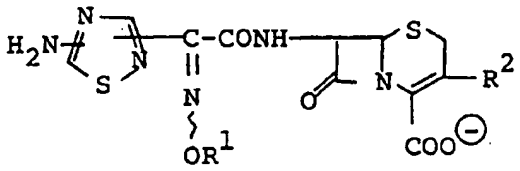
(wherein R^1 is as defined below) and the anti isomer means the other geometrical isomer having the group of the formula :



(wherein R^1 is as defined below), and in the present invention, the syn isomer is preferable.

WATER-SOLUBLE ANTIBIOTIC COMPOSITION

The water-soluble antibiotic compositions of the present invention are novel and comprise crystals of the cephem compounds of the following chemical formula :



(II)

wherein R^1 and R^2 are each as defined above, or acid addition salts thereof, and a pharmaceutically acceptable carbonic acid salt.

With regard to the definitions of the symbols R^1 and R^2 used in the cephem compound (II), suitable examples and illustration thereof which the present invention intends to include within the scope are explained in detail as follows.

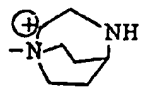
The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable aliphatic hydrocarbon may include cyclic or acyclic aliphatic hydrocarbon, such as lower alkyl, which may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, preferably one having 1 to 4 carbon atom(s); lower alkenyl, which may include straight or branched one having 2 to 6 carbon atoms, such as vinyl, allyl, 1-propenyl, 2-methylallyl, 2-butenyl, 2-pentenyl and 5-hexenyl.

The residue of an aliphatic hydrocarbon thus defined may have one or more, preferably, one to two suitable substituents. Such suitable substituent(s) may be a conventional one used in the cephalosporin field, such as carboxy, halogen (e.g. fluorine, chlorine and bromine), cyano, amino, hydroxy.

The substituent of the (lower)-alkyl at the 3rd position in the cephalosporin moiety is a 5- to 10-membered, mono or bicyclic heterocyclic group containing quaternary nitrogen atom, which may have a carbamoyl group.

Suitable example of the such group thus defined may be pyridinio, quinuclidinio or a group or the formula :



each of which may be substituted by carbamoyl.

Suitable lower alkyl moiety of the heteronio(lower)-alkyl may be a straight or branched one having 1 to 6 carbon atoms(s) such as those exemplified above.

Suitable acid addition salt of the cephem compound (II) is a conventional non-toxic, hemi-, mono- or di-pharmaceutically acceptable acid addition salt formed by, the cephem compound (II) and mono- or poly-basic acid and may include an inorganic acid addition salt (e.g., hydrochloride, sulfate.) or an organic acid addition salt (e.g. acetate), in which hydrochloride and sulfate is the most preferable.

The cephem compound (II) or an acid addition salt thereof may be in a form of its hydrate.

Suitable hydrate of the compound (II) or an acid addition salt thereof may include monohydrate, dihydrate and so on, which is usable for the preparation of the water-soluble antibiotic composition of the present invention. And more preferable one is the dihydrate of it.

A suitable pharmaceutically acceptable carbonic acid salt is alkaline metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate), alkaline metal carbonate (e.g., sodium carbonate, potassium carbonate), ammonium carbonate and ammonium hydrogencarbonate.

The proportion of the pharmaceutically acceptable carbonic acid salt relative to the cephem compound (II) or an acid addition salt thereof is not particularly restrictive, and can be selected from any one which is capable of easily dissolving the cephem compound (II) and which does not have a bad influence on patients.

The preferable proportion of the pharmaceutically acceptable carbonic acid salt to the cephem compound (II) or an acid addition salt thereof is 1:5 to 10:1 by mole ratio, which is selected depending on the kinds of the carbonic acid salts, the cephem compound (II) and the acid addition salt thereof.

Particularly, the suitable proportion of the pharmaceutically acceptable carbonic acid salt relative to the acid addition salt of the cephem compound (II) is such that the ratio of the pharmaceutically acceptable carbonic acid salt to the acid addition salt of the cephem compound (II) is substantially within the range of 0.5:1 to 4:1 equivalents and preferably 1:1 to 3:1 equivalents.

It follows that the monoacidic base such as sodium hydrogencarbonate is normally used in a proportion of 0.5 to 4 moles, preferably 1 to 2 moles per mole of the monoacid addition salt of the cephem compound (II) in case that the basicity of the acid is 1. And that the diacidic base such as sodium carbonate is normally employed within the range of 0.25 to 2 moles, preferably 0.5 to 1 moles per mole of the monoacid addition salt of the cephem compound (II) in case that the basicity of the acid is 1.

The antibiotic compositions of this invention are produced by admixing the crystals of the cephem compounds (II) or their acid addition salts with a pharmaceutically acceptable carbonic acid salt by a conventional means. In this admixing procedure, there may also be incorporated certain other known pharmaceutical additives including local anaesthetics such as lidocaine hydrochloride and mepivacaine hydrochloride The composition thus produced is usually aseptically packed into vials.

While the dosage of the active ingredient of the water-soluble antibiotic composition of the present invention will vary depending upon the age and condition of the patient, an average single dose of about 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (II) on an anhydrous compound (II) basis according to the present invention was proved to be effective for treating infectious diseases caused by pathogenic microorganisms. In general, amounts between 1 mg/body and about 6,000 mg/body or even more may be administered per day.

In the present water-soluble antibiotic composition, the acid addition salt of the cephem compound (II) is more preferable for a component of the present water-soluble antibiotic composition, because the dissolution rate of the composition comprising the acid addition salt of the cephem compounds (II) is faster than that of composition comprising the corresponding free cephem compound (II).

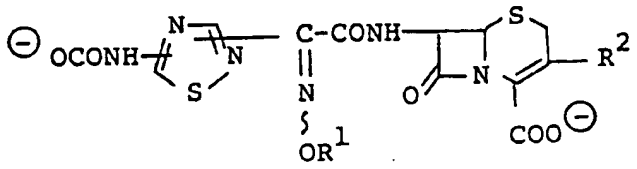
The cephem compound (II) or a salt thereof and their crystals can be prepared according to the methods described in the preparation mentioned below of this specification or in the before-mentioned, known European Patent Publications.

SALTS OF NEW CEPHEM COMPOUNDS

During the inventors' investigation on the water-soluble antibiotic composition mentioned above, they found that some type of salts of the new cephem compounds derived from the cephem compound (II) are formed in an aqueous solutions of the said compositions. And as a result of their continuous investigation, the inventors have succeeded in preparing water-soluble salts of new cephem compounds of the present invention.

The salts (I) of new cephem compounds can be represented as follows.

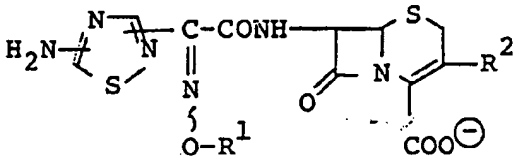
Salts (I) of the new cephem compound comprising cation(s) and anion of the formula :



wherein R^1 and R^2 are each as defined above.

With regard to the definitions of the symbols R^1 and R^2, there may be exemplified the same ones as those mentioned for the cephem compound (II).

The salts (I) of the new cephem compounds can be prepared by a process which is illustrated in the following scheme.



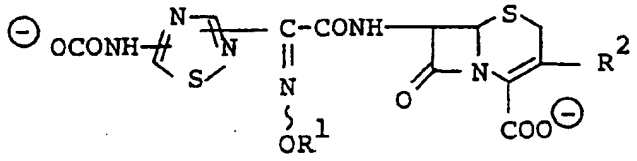
(II)

or a salt thereof

i) CO_2 in the presence of a base, or

ii) carbonic acid salt

salts (I) of the new cephem compounds comprising cation(s) and anion of the formula :



wherein R^1 and R^2 are each as defined above.

Suitable cation(s) may be pharmaceutically acceptable cation(s), such as an alkali metal cation(s) (e.g., sodium cation, potassium cation), an alkaline earth metal cation(s) (e.g., calcium cation, magnesium cation), ammonium ion(s),., and the most suitable pharmaceutically acceptable cation is sodium cation.

In case the cation is a multivalent one, it normally forms a salt with an equivalent number of anions to the valency of the cation.

Further it is to be noted that the various type of salts can be formed due to the presence of two carboxylato ions in the molecule of the object salts (I). When one of the two carboxylato ions forms a salt with one cation, the other carboxylato ion may form an intramolecular salt with a heteronio ion of R^2.

Still further, the two carboxylato ions may form salts with cations simultaneously, and in this case, the heteronio ion forms a salt with an anion from a base being used in a process of its preparation.

The process for preparing the object salts (I) is explained in detail in the following.

The object salts (I) can be prepared by reacting the compounds (II) or salts thereof with carbon dioxide in the presence of base, or with carbonic acid salt.

Suitable salts of the starting compound (II) are conventional pharmaceutically acceptable non-toxic salts and may include inorganic salts, for example, metal salts such as alkali metal salts (e.g., the sodium salt and potassium salt) and alkaline earth metal salts (e.g., the calcium salt and magnesium salt,), ammonium salts.; organic salts for example, organic amine salts (e.g., the trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylene-diamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt); organic carboxylic or sulfonic acid salts (e.g., the formate, acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate,); inorganic acid salts (e.g., the hydrochloride, hydrobromide, sulfate, phosphate); and salts with basic or acidic amino acids (e.g., arginine, aspartic acid, glutamic acid, lysine)

Carbon dioxide can be supplied by various states, such as dry ice and carbonic acid gas.

In this reaction, the cation(s) may be pharmaceutically acceptable one(s) supplied by a base used in a preparation of the object salts (I). The preferred base is an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), an alkali earth metal hydroxide (e.g., magnesium dihydroxide, calcium dihydroxide), the above alkali or alkali earth metal salt of a weak acid (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, calcium carbonate,.), or any other base which is capable of supplying pharmaceutically acceptable cation(s).

Suitable carbonic acid salts used in this reaction may be the same as those given for the pharmaceutically acceptable carbonic acid salts in the water-soluble antibiotic composition.

The reaction, is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, carbon tetrachloride, dichloromethane, dichloroethane, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction. Among the solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The object salts (I) of the present invention are novel compounds which exhibit high antibacterial activity and inhibit the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative bacteria and further, possess higher solubilities in water than the corresponding free aminothiadiazol compounds, and are therefore useful as antimicrobial agents. For therapeutic purpose, the salts according to the present invention can be used in the form of conventional pharmaceutical preparation which contain said salts, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or an inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be in solid form such as capsule, tablet, dragee, ointment or suppository, or in liquid form such as solution, suspension, or emulsion. If desired, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives, such as lactose, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

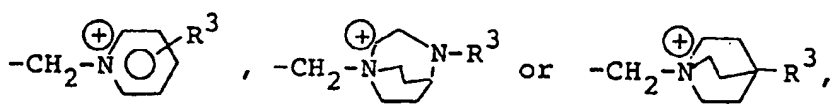
While the dosage of the salts will vary depending upon the age and condition of the patient, an average single dose of about 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the salts according to the present invention was proved to be effective for treating infectious diseases caused by pathogenic microorganisms. In general, amounts between 1 mg/body and about 6,000 mg/body or even more may be administered per day.

Preferred embodiments of the object salts (I) and the cephem compound (II) of the present invention are as follows.

Cation is a sodium cation;

R^1 is $(C_1\text{-}C_4)$alkyl (more preferably methyl, ethyl or propyl) or $(C_2\text{-}C_4)$alkenyl (more preferably allyl);

R^2 is a group of the formula ;



and

R^3 is hydrogen or carbamoyl.

Now in order to show the utility of the composition of the present invention, dissolution tests for the various types of the compositions were conducted, the results of which are shown in the following.

In the Dissolution Tests, Preparations and Examples mentioned hereinbelow,

"Nujol" is a registered trademark,

Compound A means :

Crystal of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride dihydrate (syn isomer),

Compound B means :

Crystal of 7-[2-allyloxyimino-2-(5-aminol-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer),

Compound C means :

Crystal of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer),

Compound D means :

Crystal of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer),

Compound E means :

Crystal of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer),

Compound F means:

Crystal of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hemisulfate (syn isomer), and

Compound G means:

Crystal of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer).

Dissolution Tests

[Test Samples]

The pharmaceutical preparations obtained according to Examples 1 to 11, which contain the following amounts of the Compounds A to E and carbonic acid salt, were used as Test Samples (1) to (11), respectively.

Test Sample (1)	
Compound A	50 mg
Sodium carbonate	9.3 mg

Test Sample (2)	
Compound A	50 mg
Sodium hydrogencarbonate	7.3 mg

Test Sample (3)	
Compound A	50 mg
Potassium carbonate	12 mg

Test Sample (4)	
Compound A	50 mg
Potassium hydrogencarbonate	17.4 mg

Test Sample (5)	
Compound A	50 mg
Sodium hydrogencarbonate	14.6 mg

Test Sample (6)	
Compound A	50 mg
Ammonium carbonate	18.9 mg

Test Sample (7)	
Compound A	50 mg
Ammonium hydrogencarbonate	13.8 mg

Test Sample (8)	
Compound B	50 mg
Sodium carbonate	11.9 mg

Test Sample (9)	
Compound C	50 mg
Sodium hydrogencarbonate	8.4 mg

Test Sample (10)	
Compound D	50 mg
Sodium hydrogencarbonate	22 mg

Test Sample (11)	
Compound E	50 mg
Sodium hydrogencarbonate	8.8 mg

As a comparison, the following reference samples were also tested.

Reference Sample (1)	
Compound C	50 mg

Reference Sample (2)	
Compound B	50 mg

Reference Sample (3)	
Compound E	50 mg

Reference Sample (4)	
Compound D	50 mg

[Test Method]

The velocity of dissolution of the test samples were observed after addition of distilled water into said test samples at ambient temperature, respectively.

Concentrations (w/v) of the cephem compound(II) in the dissolved test samples were provided in the parentheses.

Table 1

	Volume of Distilled Water (ml)	Velocity of Dissolution (Concentration)
Test Sample (1)	0.25	≦1 minute (20 % w/v)
Test Sample (2)	0.25	≦1 minute (20 % w/v)
Test Sample (3)	0.25	≦1 minute (20 % w/v)
Test Sample (4)	0.25	≦1 minute (20 % w/v)
Test Sample (5)	0.05	≦1 minute (100 % w/v)
Test Sample (6)	0.25	≦1 minute (20 % w/v)
Test Sample (7)	0.25	≦1 minute (20% w/v)
Test Sample (8)	0.25	≦1 minute (20 % w/v)
Test Sample (9)	0.25	≦A few hours (20% w/v)
Reference Sample (1) *1	0.25	Slightly soluble
Reference Sample (2) *2	0.25	Slightly soluble

Note

*1: Maximum concentration of this sample dissolved in water was 4.07 % (w/v).

*2: Maximum concentration of this sample dissolved in water was 8.28 % (w/v).

Table 2

	Volume of Distilled Water (ml)	Velocity of Dissolution (Concentration)
Test Sample (10)	0.25	≦1 minute (20 % w/v)
Test Sample (11)	0.25	≦A few hours (20 % w/v)
Reference Sample (3) *3	0.25	Slightly soluble
Reference Sample (4) *4	0.25	Slightly soluble

Note

*3: Maximum concentration of this sample dissolved in water was 2 % (w/v).

*4: Maximum concentration of this sample dissolved in water was 10% (w/v).

And, further, in order to show the utility of the salts(I) of new cephem compounds , with regard to a representative salt of this invention, the test data on the in vitro anti-bacterial activity are shown in the following.

Test Salt

Sodium 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer).

Test Method

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of test strain in Trypticase-soy broth (10^6 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of test salt, and minimal inhibitory concentration (MIC) was expressed in terms of μg/mℓ after incubation at 37 °C for 20 hours.

Test Result

MIC (μg/mℓ)	
Test Strains	Test salt
P. aeruginosa 26	0.390

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

To a solution of 1,4-diazabicyclo[3.2.2]nonane (2.75 g) in a mixture of tetrahydrofuran (40 ml) and water (20 ml) was added potassium cyanate (2.65 g) at ambient temperature. The mixture was adjusted to pH 5.0 with concentrated hydrochloric acid and stirred at 50 °C for 40 minutes. The mixture was poured into 50% aqueous solution of potassium hydroxide. The resulted aqueous solution was extracted with chloroform. The extract was dried over anhydrous potassium carbonate and evaporated to dryness in vacuo. The crystalline residue was recrystallized from diethyl ether to give 4-carbamoyl-1,4-diazabicyclo[3.2.2]nonane (898.5 mg).
mp : 125 to 130 °C
IR (Nujol) : 1640, 1585 cm^{-1}
NMR ($CDCl_3$, δ) : 1.50-2.30 (4H, m), 2.90-3.40 (6H, m), 3.50-3.80 (2H, m), 4.05 (1H, m), 4.73 (2H, m)
Mass : m/z 169 (M^+)

Preparation 2

1) To a mixed solution of dichloromethane (1000 ml) and tetrahydrofuran (200 ml) were added 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetyl chloride (syn isomer) (64 g) and benzhydryl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (100 g) at -15 °C. The mixture was stirred at -15 °C for one hour. The reaction mixture was poured into ice-cooled water, and neutralized with sodium hydrogencarbonate. The organic layer was separated, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether to give benzhydryl 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer) (130.5 g)
NMR (DMSO-d_6, δ) : 3.2-3.8 (2H, m), 3.93 (3H, s), 4.43 (2H, s), 5.27 (1H, d, J = 5Hz), 5.97 (1H, dd, J = 5Hz, 8Hz), 7.00 (1H, s), 7.20-7.70 (10H, m), 8.17 (2H, s), 9.70 (1H, d, J = 8Hz)

2) To a solution of benzhydryl 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer) (3 g) in dichloromethane (6 ml) and anisole (3 ml) was added dropwise trifluoroacetic acid (6 ml) at 0 °C. The mixture was stirred at 0 °C for two hours. The mixture was poured into a chilled mixture of diisopropyl ether and n-hexane (1:1, V/V). The precipitates were collected by filtration and dried under reduced pressure to give 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylic acid trifluoroacetate (syn isomer) (2.50 g).
IR (Nujol) : 1770, 1630, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 3.63 (2H, m), 3.93 (3H, s), 4.57 (2H, s), 5.18 (1H, d, J = 5Hz), 5.83 (1H, dd, J = 5Hz, 8Hz), 8.10 (2H, broad s), 9.55 (1H, d, J = 8Hz)

Preparation 3

To a solution of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylic acid trifluoroacetate (syn isomer) (1.03 g) in N,N-dimethylformamide (20 ml) was added 4-carbamoyl-1,4-diazabicyclo[3.2.2]nonane (800 mg) at 0 °C. The mixture was stirred for 20 minutes at 0 °C. The mixture was poured into ethyl acetate (150 ml). The precipitates were collected by filtration and dried under reduced pressure. The solid was dissolved in water (50 ml) and chromatographed on non-ionic adsorption resin "Diaion HP-20" (Trademark, maker; Mitsubishi Chemical Industries) (40 ml) eluting with 5% isopropyl alcohol in water. The desired fractions were collected and lyophilized to give 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-carbamoyl-1,4-diazabicyclo[3.2.2]nonan-1-ylio]methyl-3-cephem-4-carboxylate (syn isomer) (359 mg).
mp : 140 °C (dec.)
IR (Nujol) : 1770, 1660, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-4.50 (17H, m), 3.92 (3H, s), 5.15 (1H, d, J = 5Hz), 5.50-6.10 (3H, m), 8.10 (2H, s), 9.50 (1H, d, J = 8Hz)
Mass : m/z 566 (M^+)

Preparation 4

To a solution of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-carbamoyl-1,4-diazabicyclo[3.2.2]nonan-1-ylio]methyl-3-cephem-4-carboxylate (syn isomer) (8.03 g) in water (8.03 ml) was added 2N sulfuric acid (8.03 ml) at ambient temperature. The solution was allowed to stand for one hour. The colorless crystals were collected by filtration, washed with cooled water and acetone, and dried over

phosphorus pentoxide to give colorless crystals of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-carbamoyl-1,4-diazabicyclo[3.2.2]nonan-1-ylio]methyl-3-cephem-4-carboxylate sulfate (syn isomer) (6.18 g).
mp : 180 °C (dec.)
IR (Nujol) : 1795, 1645, 1540 cm^{-1}
NMR (D_2O, δ) : 2.05-2.70 (4H, m), 3.30-4.40 (13H, m), 4.10 (3H, s), 5.35 (1H, d, J=5Hz), 5.85 (1H, d, J=5Hz)

Preparation 5

The crystals of the following compound were obtained according to a similar manner to that of Preparation 4.
7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(4-carbamoyl-1-quinuclidinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer)
mp : 170-175 °C (dec.)
IR (Nujol) : 1800, 1660, 1620, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 1.70-2.40 (6H, m), 3.00-4.80 (10H, m), 3.95 (3H, s), 5.28 (1H, d, J=5Hz), 5.90 (1H, dd, J=5Hz, 8Hz), 7.0-7.5 (2H, m), 8.13 (2H, s), 9.60 (1H, d, J=8Hz)

Preparation 6

1) To a suspension of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (6.87 g) in water (200 ml) was added 1N hydrochloric acid (17.5 ml) at ambient temperature.
The aqueous solution was lyophilized to give colorless powder (6.4 g). The powder was dissolved in water (6.4 ml) and the solution was allowed to stand for 3 hours at ambient temperature. The precipitated crystals were collected by filtration, washed with cooled water and ethanol, and dried over phosphorus pentoxide in vacuo to give a mixture of colorless crystals of anhydride and dihydrate of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride(syn isomer)(2.10 g).
mp : 175 °C (dec.)
IR (Nujol) : 1755, 1705, 1655, 1605 cm^{-1}
NMR (DMSO-d_6, δ) : 3.37, 3.60 (2H, ABq, J=18Hz), 4.63 (2H, m), 5.00-5.27 (3H, m), 5.40 (1H, m), 5. 60 (2H, m), 5.70-6.20 (2H, m), 8.00-8.40 (4H, m), 8.67 (1H, t, J=8Hz), 9.10 (1H, d, J=5Hz), 9.60 (1H, d, J=8Hz)
Elemental analysis
Found: C, 43.13; H, 3.88; N, 17.76; S, 11.85; Cl, 6.25;
2) The mixture of the crystals of anhydride and dihydrate of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (2 g) was allowed to stand for 3 days over saturated aqueous potassium nitrate to give the crystals of 7-[2-allyloxyimino-2-(5-amino-1,2,4- thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem- 4-carboxylate hydrochloride dihydrate (syn isomer) (2.07 g).
mp : 175 °C (dec)
IR (Nujol) : 1755, 1705, 1655, 1605 cm^{-1}
NMR (DMSO-d_6, δ) : 3.37, 3.60 (2H, ABq, J=18Hz), 4.63 (2H, m), 5.00-5.27 (3H, m), 5.40 (1H, m), 5.60 (2H, m), 5.70-6.20 (2H, m), 8.00-8.40 (4H, m), 8.67 (1h, t, J=8Hz), 9.10 (1H, d, J=5Hz), 9.60 (IH, d, J=8Hz)
Water content : 6.69 % (Karl-Fischer method)

Preparation 7

A solution of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (2 g) in 2N sulfuric acid (2.1 ml) was lyophilized to give powder. The powder was dissolved in water (2.41 ml), and the solution was allowed to stand for 12 hours at 5 °C.
The precipitated crystals were collected by filtration and air-dried to give colorless crystals of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) (0.65 g).
IR (Nujol) : 1788, 1640, 1538 cm^{-1}

NMR (D_2O, δ) : 8.98 (2H, d, J = 6Hz), 8.63 (1H, t, J = 7Hz), 8.14 (2H, t, J = 6Hz), 5.96 (1H, d, J = 5Hz), 5.89-5.32 (2H, dd, J = 15Hz), 5.34 (1H, d, J = 5Hz), 4.08 (3H, s), 3.86-3.38 (2H, dd, J = 18Hz)

Preparation 8

The crystals of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride dihydrate (syn isomer) (10 g) was dried over phosphorus pentoxide under reduced pressure to give the crystals of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (9.4 g).
mp : 175 • C (dec.)
IR (Nujol) : 3400, 3275, 3175, 2200, 1790, 1700, 1660, 1025, 1015 cm^{-1}
NMR (DMSO-d_6, δ) : 3.47 (2H, m), 4.63 (2H, m), 5.00-5.27 (3H, m), 5.40 (1H, m), 5.60 (2H, m), 5.70-6.20 (2H, m), 8.00-8.40 (4H, m), 8.67 (1H, t, J = 8Hz), 9.10 (1H, d, J = 5Hz), 9.60 (1H, d, J = 8Hz)

Preparation 9

The crystals of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride dihydrate (syn isomer) were obtained according to a similar manner to that of Preparation 6.
IR (Nujol) : 1760, 1705, 1660, 1615, 1590, 1540, 1520 cm^{-1}
NMR (D_2O-NaOD, δ) : 0.90 (3H, t, J = 8Hz), 1.70 (2H, m), 3.17, 3.63 (2H, ABq, J = 18Hz), 4.20 (2H, t, J = 8Hz), 5.23 (1H, d, J = 5Hz), 5.28, 5.55 (2H, ABq, J = 15Hz), 5.85 (1H, d, J = 5Hz), 8.00 (2H, t, J = 7Hz), 8.50 (1H, t, J = 7Hz), 8.90 (2H, d, J = 7Hz)
Water content : 7.94 % (Karl-Fisher method)

Preparation 10

7-[2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (9.1 g) was dissolved with water (18 ml). The solution was stood for 4 hours at ambient temperature. The precipitated crystals were collected by filtration, washed with cold water, and dried over phosphorus pentoxide in vacuo to give colorless crystals of the above compound.
mp : 205-210 • C (dec.)
IR (Nujol) : 1795, 1660, 1640, 1620 cm^{-1}
NMR (DMSO-d_6-D_2O, δ) : 3.02, 3.46 (2H, J = 18Hz), 4.62 (2H, m), 5.06 (1H, d, J = 5Hz), 5.10-5.50 (4H, m), 5.71 (1H, d, J = 5Hz), 5.80-6.00 (1H, m), 7.94 (2H, t, J = 6Hz), 8.44 (1H, t, J = 6Hz), 8.90 (1H, d, J = 6Hz)

Preparation 11

7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (2 g) was dissolved in water (1 ml), and the solution was stood for 1 hour in refrigerator to give colorless crystals. Filtration and washing with acetone followed by ether gave colorless crystals of the above compound.
IR (Nujol) : 1780, 1670, 1610 cm^{-1}
NMR (DMSO-d_6-D_2O, δ) : 9.30 (2H, d, J = 6Hz), 8.61 (1H, t, J = 7Hz), 8.14 (2H, t, J = 7Hz), 5.80-5.53 (2H, m), 5.30-5.03 (2H, m), 3.93 (3H, s), 3.67-2.97 (2H, dd, J = 17Hz)

Preparation 12

1) 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (4 g) was dissolved in 0.2 N sulfuric acid (40 ml). The mixture was lyophilized to give 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hemisulfate (syn isomer) (4.1 g).
IR (Nujol): 1770, 1640, 1620 cm^{-1}
NMR (DMSO-d_6,δ): 3.20, 3.50 (2H, ABq, J = 18 Hz), 4.60 (2H, m), 5.00-5.60 (4H, m), 5.10 (1H, d, J = 5Hz), 5.70-6.10 (1H, m), 5.77 (1H, dd, J = 5Hz, 8Hz), 8.00-8.30 (4H, m), 8.60 (1H, t, J = 7Hz), 9.15 (2H, d, J = 7Hz), 9.55 (1H, d, J = 8Hz)
2) The crystals of 7-[2-allyloxyimino -2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hemisulfate (syn isomer) was obtained according to a similar manner to that of

Preparation 10.

NMR (DMSO-d_6,δ): 3.20, 3.50 (2H, ABq, J = 18 Hz), 4.60 (2H, m), 5.00-5.60 (4H, m), 5.10 (1H, d, J = 5Hz), 5 70-6.10 (1H, m), 5.77 (1H, dd, J = 5Hz, 8Hz), 8.00-8.30 (4H, m), 8.60 (1H, t, J = 7Hz), 9.15 (2H, d, J = 7Hz), 9.55 (1H, d, J = 8Hz)

3) 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (5 g) was dissolved in 1 M sulfuric acid (5 ml) at ambient temparature. Isopropyl alcohol (50 ml) was added to the mixture. The mixture was stirred for 2 hours at ambient temparature. The precipitated crystals were collected by filtration, washed with isopropyl alcohol, and dried over phosphorus pentoxide in vacuo to give the crystals of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hemisulfate (solvate of 1/2 isopropyl alcohol) (syn isomer) (5 g).

IR (Nujol): 1775, 1640, 1620 cm^{-1}

NMR (DMSO-d_6,δ): 1.15 (3H, d, J = 6Hz), 3.23, 3.70 (2H, ABq, J = 18 Hz), 4.00 (0.5H, m), 4.70 (2H, m), 5.00-5.50 (5H, m), 5.50-6.20 (2H, m), 8.07 (2H, t, J = 7Hz), 8.57 (1H, t, J = 8Hz),8.93 (2H, d, J = 7Hz) (1H, d, J = Hz),

Preparation 13

1) 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (4 g) was dissolved in 0.4 N sulfuric acid (40 ml). The mixture was lyophilized to give 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) (4.20 g).

IR (Nujol): 1770, 1640, 1620 cm^{-1}

NMR (DMSO-d_6,δ): 3.20, 3.50 (2H, ABq, J = 18 Hz), 4.60 (2H, m), 5.00-5.60 (4H, m), 5.10 (1H, d, J = 5Hz), 5.70-6.10 (1H, m), 5.77 (1H, dd, J = 5Hz, 8Hz), 8.00-8.30 (4H, m), 8.60 (1H, t, J = 7Hz), 9.15 (2H, d, J = 7Hz), 9.55 (1H, d, J = 8Hz)

2) The crystals of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) was obtained according to a similar manner to that of Preparation 10.

NMR (DMSO-d_6,δ): 3.20, 3.50 (2H, ABq, J = 18 Hz), 4.60 (2H, m), 5.00-5.60 (4H, m), 5.10 (1H, d, J = 5Hz), 5.70-6.10 (1H, m), 5.77 (1H, dd, J = 5Hz, 8Hz), 8.00-8.30 (4H, m), 8.60 (1H, t, J = 7Hz), 9.15 (2H, d, J = 7Hz), 9.55 (1H, d, J = 8Hz)

Preparation 14

7-[2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (4 g) was dissolved in 0.2N hydrochloric acid (40 ml). The mixture was lyophilized to give 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (4.0 g).

IR (Nujol): 1770, 1660, 1610 cm^{-1}

NMR (DMSO-d_6,δ): 3.30, 3.63 (2H, ABq, J = 18 Hz), 4.60 (2H, m), 4.70-5.70 (8H, m), 5.70-6.10 (1H, m), 8.00-8.40 (4H, m), 8.60 (1H, t, J = 7Hz), 9.20 (2H, d, J = 6Hz), 9.60 (1H, d, J = 8Hz)

Preparations of water-soluble antibiotic compositions

Example 1

Components	mole equivalent
Compound A	1
Sodium carbonate	1

The above-mentioned components were aseptically mixed, and the aseptic mixture was packed into sterilized dry vial to obtain a pharmaceutical preparation for injection.

The pharmaceutical preparations for injection comprising the following components were obtained according to a similar way to that of Example 1.

Example 2

Components	mole equivalent
Compound A	1
Sodium hydrogencarbonate	1

Example 3

Components	mole equivalent
Compound A	1
Potassium carbonate	1

Example 4

Components	mole equivalent
Compound A	1
Potassium hydrogencarbonate	2

Example 5

Components	mole equivalent
Compound A	1
Sodium hydrogencarbonate	2

Example 6

Components	mole equivalent
Compound A	1
Ammonium carbonate	2

Example 7

Components	mole equivalent
Compound A	1
Ammonium hydrogencarbonate	2

Example 8

Components	mole equivalent
Compound B	1
Sodium carbonate	1

Example 9

Components	mole equivalent
Compound C	1
Sodium hydrogencarbonate	1

Example 10

Components	mole equivalent
Compound D	1
Sodium hydrogencarbonate	3

Example 11

Components	mole equivalent
Compound E	1
Sodium hydrogencarbonate	1

Example 12

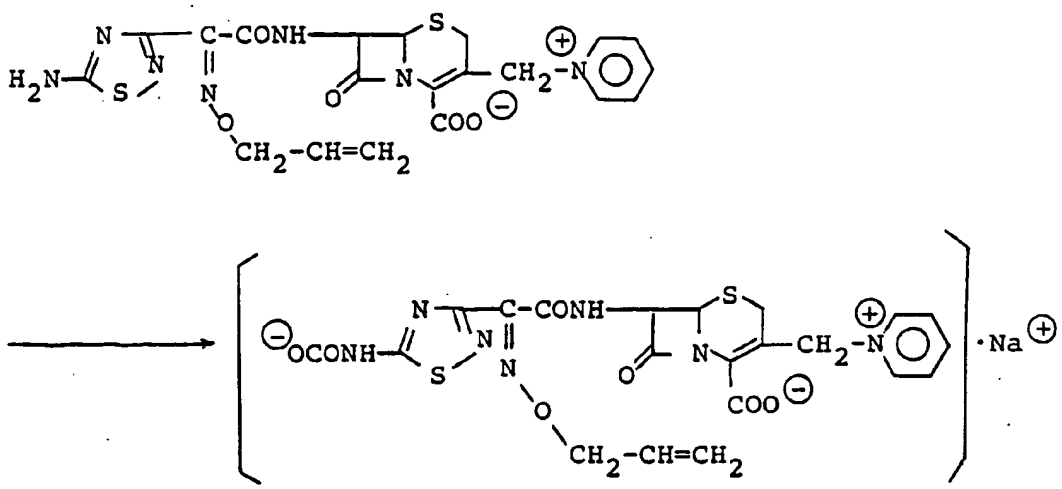
Components	mole equivalent
Compound F	1
Sodium hydrogencarbonate	2

Example 13

Components	mole equivalent
Compound G	1
Sodium hydrogencarbonate	3

Preparations of the salts of new cephem compound

Example 14



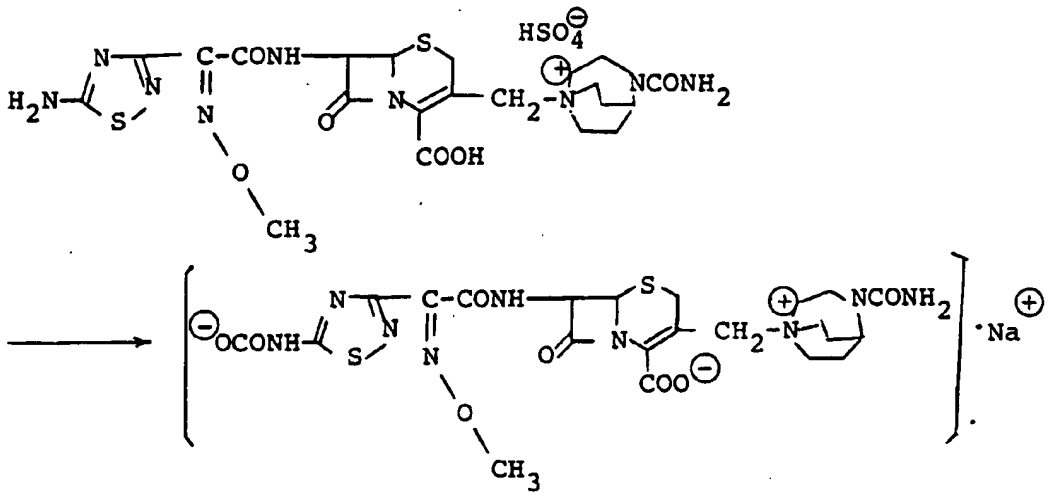
To a solution of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (1.15 g) in 50% aqueous acetone (9.2 ml) was added sodium hydrogencarbonate (193 mg) and dry ice (4.4 g) at room temperature. The mixture was stirred in a sealed tube for 5 hours. Acetone was removed under reduced pressure. The residual solution was chromatographed on non-ionic adsorption resin "Diaion HP-20" (Trademark, maker : Mitsubishi Chemical Industries) eluting with water. The desired fractions were collected and lyophilized to give sodium 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (500 mg).

IR (Nujol) : 3500-3100, 1765, 1660, 1610, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 4.6 (2H, m), 5.10 (1H, d, J=5Hz), 5.2 (2H, m), 5.33 and 5.53 (2H, ABq, J=12Hz), 5.76 (1H, dd, J=5Hz, 8Hz), 5.8-6.2 (1H, m), 8.10 (2H, t, J=6Hz), 8.55 (1H, m), 9.40 (3H, m), 10.1 (1H, broad s)

FAB Mass : m/z 569 (M + 1)

Example 15



Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-carbamoyl-1,4-diazabicyclo[3.2.2]nonan-1-ylio]methyl-3-cephem-4-carboxylate (syn isomer) (463 mg) was obtained by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-carbamoyl-1,4-diazabicyclo-[3.2.2]nonan-1-ylio]methyl-3-cephem-4-carboxylate sulfate (syn isomer) (1 g) with sodium hydrogencarbonate (379 mg) and dry ice (4 g) according to a similar manner to that of Example 14.

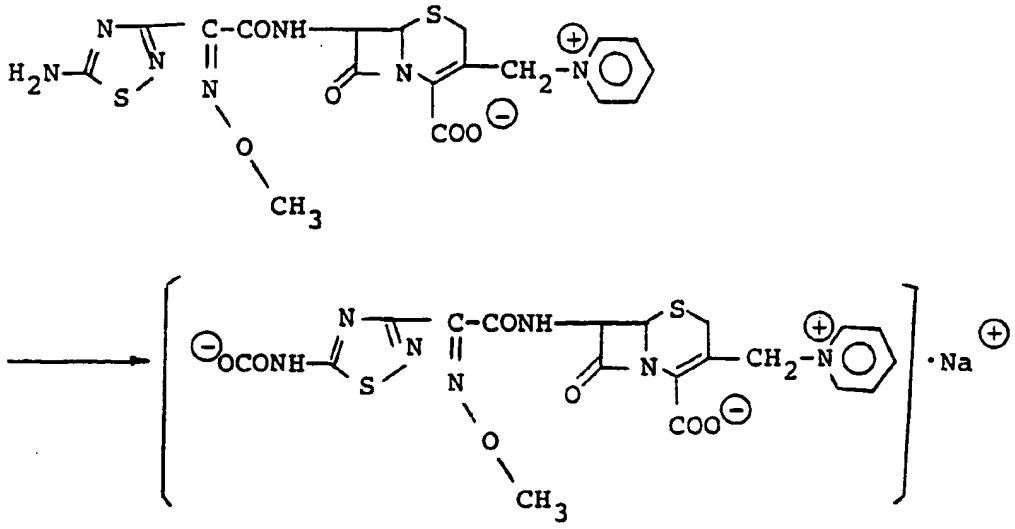
mp : 140 • C (dec.)

IR (Nujol) : 1770, 1660, 1620 cm^{-1}

NMR (D_2O, δ) : 2.0-2.6 (4H, m), 2.8-3.20 (1H, m), 3.25-4.25 (12H, m), 4.10 (3H, s), 5.35 (1H, d, J = 5Hz), 5.90 (1H, d, J = 5Hz)

NMR (DMSO-d_6, δ) : 1.80-2.30 (4H, m), 2.70-4.40 (13H, m), 3.92 (3H, s), 5.10 (1H, d, J = 5Hz), 5.70 (1H, m), 6.12 (2H, m), 9.50 (1H, m), 9.90 (1H, s)

Example 16

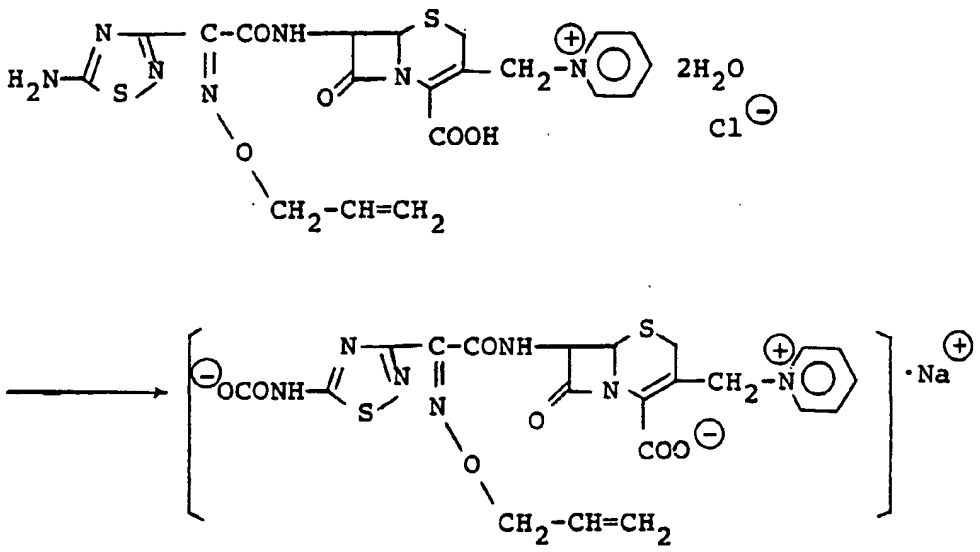


Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (550 mg) was obtained by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) (2.09 g) with sodium hydrogencarbonate (1.11 g) and dry ice (8.36 g) according to a similar manner to that of Example 14.

IR (Nujol) : 1755 cm^{-1}

NMR (DMSO-d_6, δ) : 9.78 (1H, s), 9.47 (2H, d, J=6Hz), 8.59 (1H, t, J=7Hz), 8.16 (2H, t, J=6Hz), 5.82-5.03 (3H, m), 5.06 (1H, d, J=7Hz), 3.86 (3H, s), 3.63-2.92 (2H, dd, J=18Hz)

Example 17

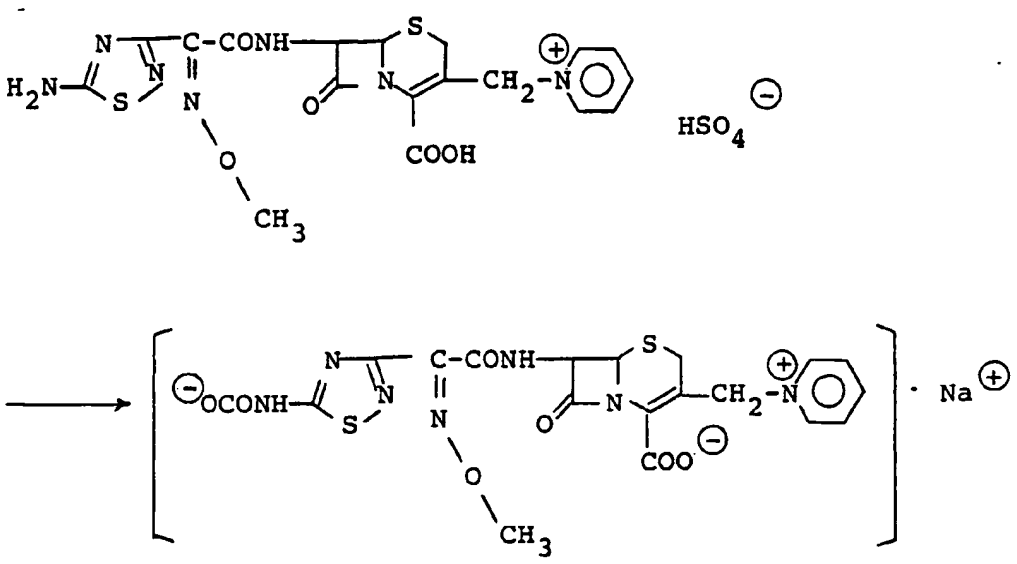


To a mixture of 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride dihydrate (syn isomer) (50 mg) and sodium hydrogencarbonate (14.6 mg) was added water (0.25 ml) at ambient temperature. Carbon dioxide was generated and the mixture became homogeneous solution.

The solution was subjected to high performance liquid chromatography. Elution was carried out using a column (4 mmØ x 25 cm) with "Lichrosorb RP-18" (Trademark, maker; Merk & Co) as a carrier and a mixture of acetonitrile and 16.4 mM phosphate buffer (pH 7) (1:9 V/V) as a mobile phase under flow rate of 1 ml/minute.

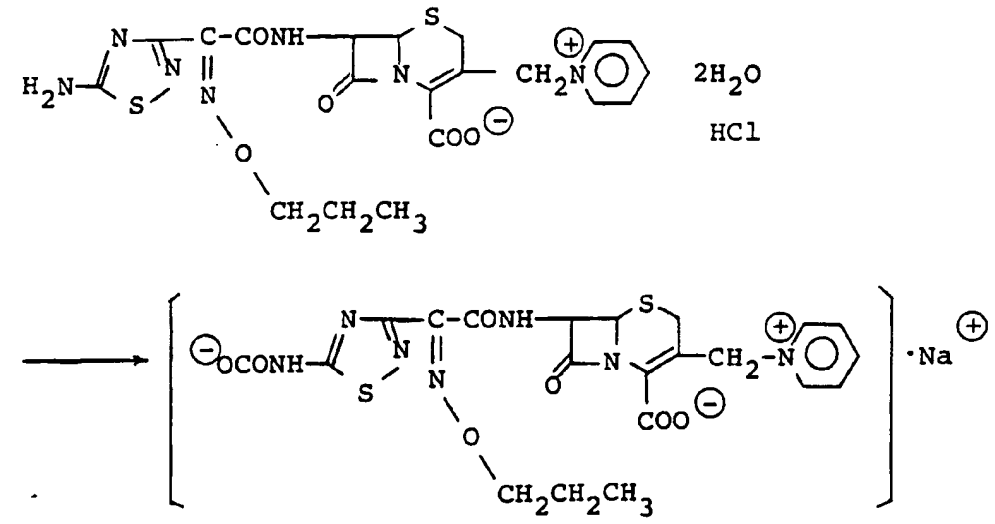
Sodium 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-(l-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) was detected by monitoring with UV detector at 254 nm.

Example 18



Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) was prepared by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) (50 mg) and sodium hydrogencarbonate (22 mg) and detected according to a similar manner to that of Example 17.

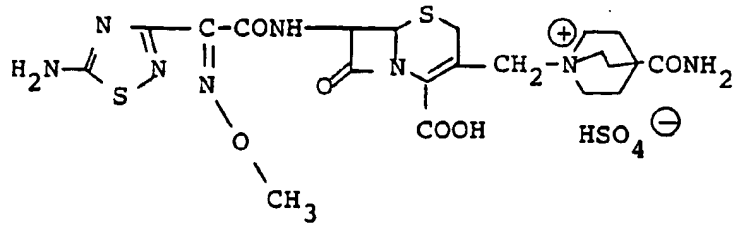
Example 19

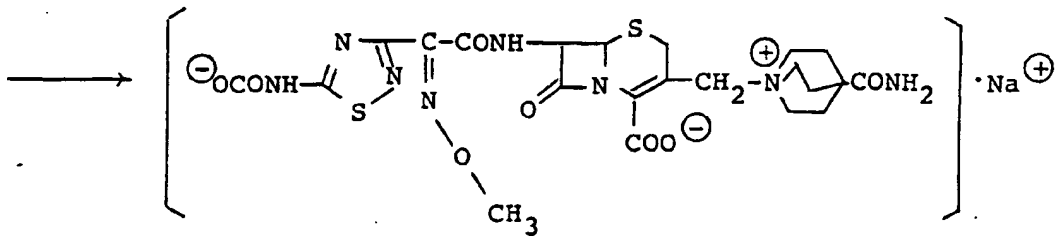


Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)-methyl-3-cephem-4-carboxylate (syn isomer) (141.5 mg) was obtained by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride dihydrate (syn isomer) (100 mg) and sodium hydrogencarbonate (29 mg) according to a similar manner to that of Example 17.

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J = 8Hz), 1.63 (2H, m), 3.04, 3.56 (2H, ABq, J = 17Hz), 4.02 (2H, t, J = 6Hz), 5.05 (1H, d, J = 5Hz), 5.17, 5.68 (2H, ABq, J = 13Hz), 8.10 (3H, m), 8.53 (1H, t, J = 8Hz), 9.40 (2H, m), 9.83 (1H, s)

Example 20



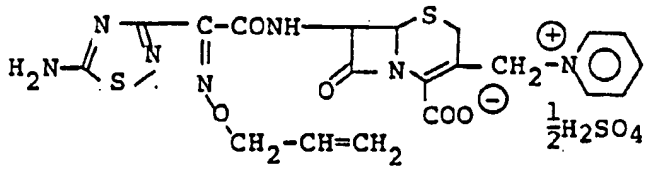


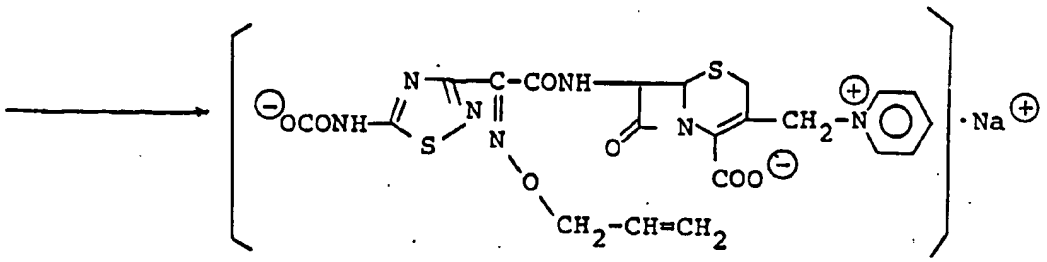
To a suspension of crystals of 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(4-carbamoyl-1-quinuclidinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) (500 mg) in 50% aqueous acetone (4 ml) was added sodium hydrogencarbonate (323 mg) at ambient temperature. Carbonic acid gas was bubbled into the mixture for four hours and diluted with water. The resulting mixture was chromatographed on non-ionic adsorption resin "Diaion HP-20" (50 ml) eluting with water. The desired fractions were collected and lyophilized to give sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(4-carbamoyl-1-quinuclidinio)methyl-3-cephem-4-carboxylate (syn isomer) (239.6 mg).

IR (Nujol) : 1765, 1650, 1610, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.70-2.20 (6H, m), 3.0-4.0 (10H, m), 3.90 (3H, s), 5.10 (1H, d, J = 5Hz), 5.67 (1H, m), 7.00-7.50 (2H, m), 9.25-9.65 (1H, m), 9.98 (1H, s)

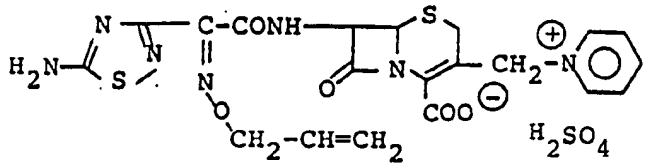
Example 21

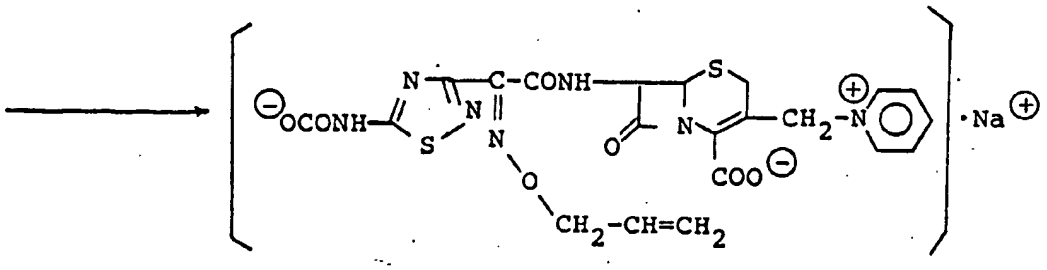




Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2- allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) was prepared by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hemisulfate (syn isomer) (50 mg) and sodium hydrogencarbonate (15.3 mg) and detected according to a similar manner to that of Example 17.

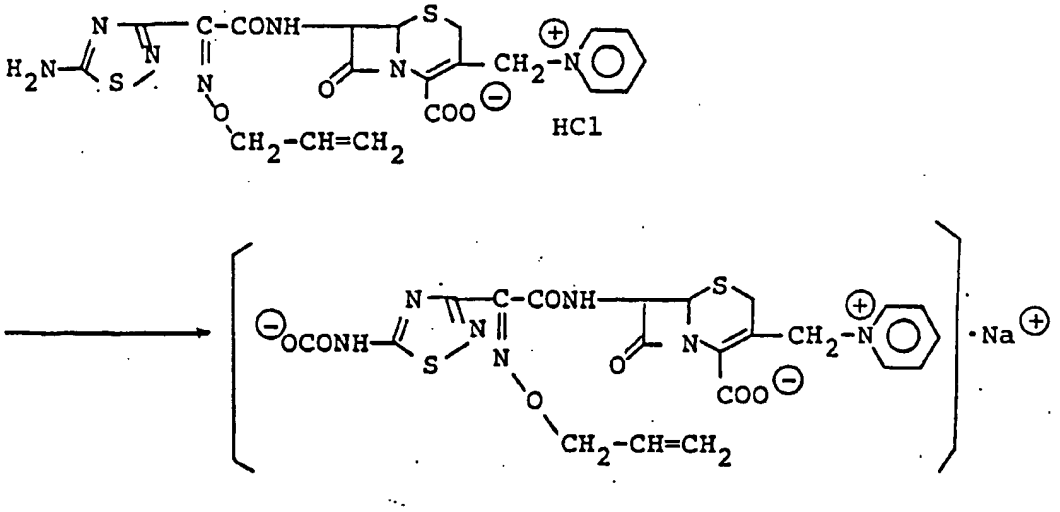
Example 22





Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)2- allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) was prepared by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate sulfate (syn isomer) (50 mg) and sodium hydrogencarbonate (21 mg) and detected according to a similar manner to that of Example 17.

Example 23

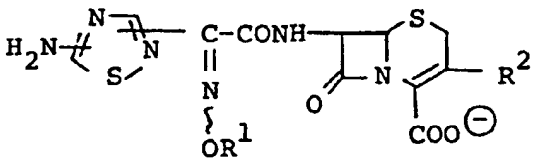


Sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)2- allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer) was prepared by reacting 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-allyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (50 mg) and sodium hydrogencarbonate (15.6 mg) and detected according to a similar manner to that of Example 17.

Claims

Claims for the following Contracting States: AT, BE, CH, LI, DE, FR, GB, IT, NL, LU, SE

1. A water-soluble antibiotic composition which comprises crystals of a cephem compound of the following formula :



wherein

R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s), and

R^2 is $(C_1\text{-}C_6)$alkyl substituted with a 5- to 10-membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom, which may have a carbamoyl group on the 5- to 10-membered mono- or bicyclic heterocyclic ring

or an acid addition salt thereof, and a pharmaceutically acceptable carbonic acid salt.

2. A water-soluble antibiotic composition of the Claim 1, wherein the cephem compound is in a form of the acid addition salt.

3. A water-soluble antibiotic composition of the Claim 2, wherein the ratio of the acid addition salt of the cephem compound to the carbonic acid salt is 1:0.5 to 1:4 equivalents.

4. A water-soluble antibiotic composition of the Claim 3, wherein the ratio of the acid addition salt of the cephem compound to the carbonic acid salt is 1:1 to 1:3 equivalents.

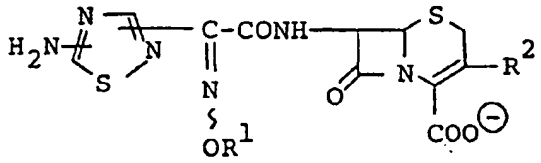
5. A water-soluble antibiotic composition of the Claim 4, wherein R^1 is C_1-C_6 alkyl or C_2-C_6 alkenyl, R^2 is 1-pyridiniomethyl, and the pharmaceutically acceptable carbonic acid salt is alkali metal hydrogencarbonate or alkali metal carbonate.

6. A water-soluble antibiotic composition of the Claim 5, wherein R^1 is allyl or propyl.

7. A water-soluble antibiotic composition of the Claim 6, wherein the acid addition salt of the cephem compound is 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) or its dihydrate.

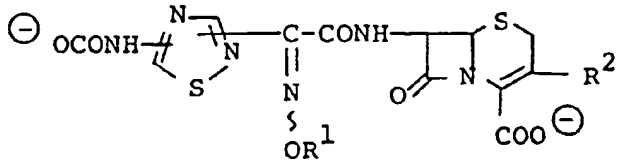
8. A water-soluble antibiotic composition of the Claim 7, wherein alkali metal hydrogencarbonate is sodium hydrogencarbonate, and the ratio of the acid addition salt of the cephem compound to sodium hydrogencarbonate is 1:1 equivalent.

9. A process for preparing a water-soluble antibiotic composition which comprises admixing crystals of the cephem compound of the following formula :



wherein R^1 and R^2 are each as defined in Claim 1, or an acid addition salt thereof, and a pharmaceutically acceptable carbonic acid salt.

10. A salt comprising cation(s) and anion of the formula :

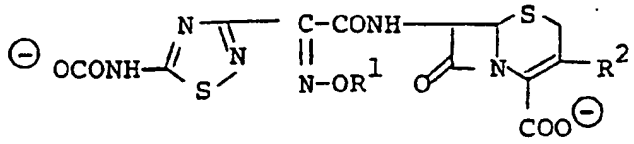


wherein

R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s),

R^2 is (C_1-C_6)alkyl substituted with a 5- to 10-membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom which may have a carbamoyl group on the 5- to 10-membered mono- or bicyclic heterocyclic ring.

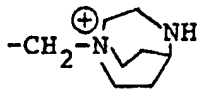
11. A salt of the Claim 10, wherein the anion is represented by the following formula :



wherein

R^1 is C_1-C_6 alkyl or C_2-C_6 alkenyl and

R^2 is 1-pyridiniomethyl, quinuclidiniomethyl, or a group of the formula :



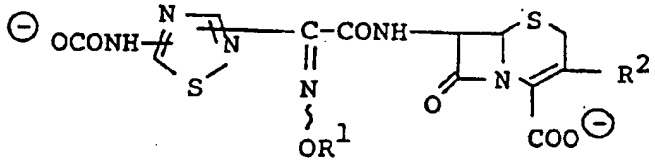
each of which may be substituted by carbamoyl.

12. A salt of the Claim 11, wherein
R^2 is 1-pyridiniomethyl, and the cation is an alkali metal.

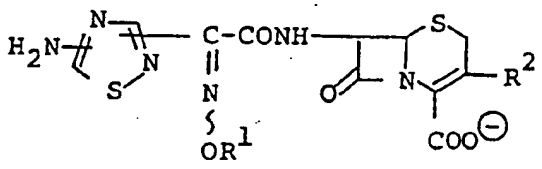
13. A salt of the Claim 12, which is sodium 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer).

14. A salt of the Claim 12, which is sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer).

15. A process for preparing a salt comprising cation(s) and anion of the formula :



wherein
R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s),
R^2 is $(C_1\text{-}C_6)$alkyl substituted with a 5- to 10-membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom which may have a carbamoyl group on the 5- to 10-membered mono- or bicyclic heterocyclic ring,
which comprises reacting a cephem compound of the formula :



wherein R^1 and R^2 are each as defined above,
or a salt thereof,
with carbon dioxide in the presence of base or with carbonic acid salt.

16. A pharmaceutical composition comprising a salt of Claim 10 thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

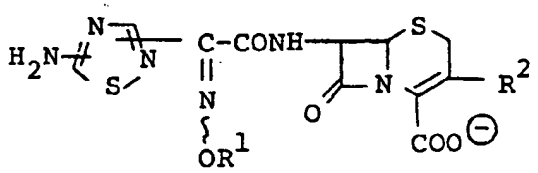
17. A use of a salt of claim 10 for manufacture of medicament for treating or preventing infectious diseases.

18. A salt of claim 10 for use as a medicament.

19. A salt of claim 10 for use in treating or preventing infectious diseases.

Claims for the following Contracting States: ES, GR

1. A process for preparing a water-soluble antibiotic composition which comprises admixing crystals of the cephem compound of the following formula :



wherein

R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s), and

R^2 is $(C_1\text{-}C_6)$alkyl substituted with a 5- to 10-membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom which may have a carbamoyl group on the 5- to 10-membered mono- or bicyclic heterocyclic ring

or an acid addition salt thereof, and a pharmaceutically acceptable carbonic acid salt.

2. The process of the claim 1, wherein the cephem compound is in a form of the acid addition salt.

3. The process of the Claim 2, wherein the ratio of the acid addition salt of the cephem compound to the carbonic acid salt is 1:0.5 to 1:4 equivalents.

4. The process of the Claim 3, wherein the ratio of the acid addition salt of the cephem compound to the carbonic acid salt is 1:1 to 1:3 equivalents.

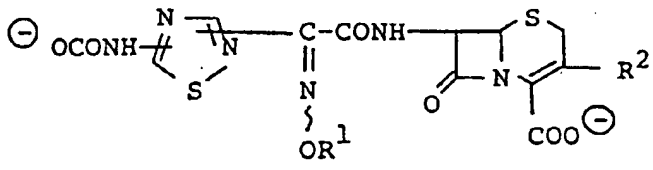
5. The process of the Claim 4, wherein R^1 is $C_1\text{-}C_6$ alkyl or $C_2\text{-}C_6$ alkenyl, R^2 is 1-pyridiniomethyl, and the pharmaceutically acceptable carbonic acid salt is alkali metal hydrogencarbonate or alkali metal carbonate.

6. The process of the Claim 5, wherein R^1 is allyl or propyl.

7. The process of the Claim 6, wherein the acid addition salt of the cephem compound is 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) or its dihydrate.

8. The process of the Claim 7, wherein alkali metal hydrogencarbonate is sodium hydrogencarbonate, and the ratio of the acid addition salt of the cephem compound to sodium hydrogencarbonate is 1:1 equivalent.

9. A process for preparing a salt comprising cation(s) and anion of the formula :

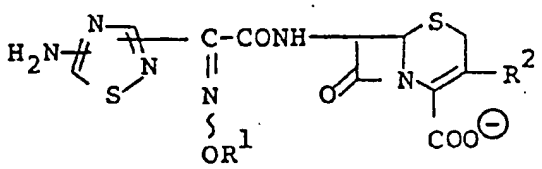


wherein

R^1 is a residue of an aliphatic hydrocarbon which may have suitable substituent(s),

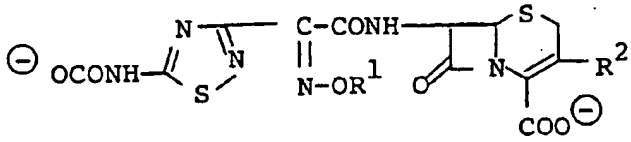
R^2 is $(C_1\text{-}C_6)$alkyl substituted with a 5- to 10- membered mono- or bicyclic heterocyclic group containing a quaternary nitrogen atom which may have a carbamoyl group on the 5- to 10-

membered mono-or bicyclic heterocyclic ring
which comprises reacting a cephem compound of the formula :

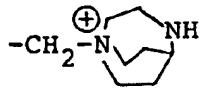


wherein R^1 and R^2 are each as defined above,
or a salt thereof,
with carbon dioxide in the presence of base, or with carbonic acid salt.

10. The process of the Claim 9, wherein the anion is represented by the following formula :



wherein
R^1 is C_1-C_6 alkyl or C_2-C_6 alkenyl and
R^2 is 1-pyridiniomethyl, quinuclidiniomethyl, or a group of the formula :



each of which may be substituted by carbamoyl.

11. The process of the Claim 10, wherein R^2 is 1-pyridiniomethyl, and the cation is an alkali metal.

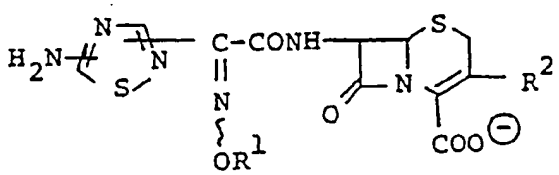
12. The process of the Claim 11, wherein the salt is sodium 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer).

13. The process of the Claim 11, wherein the salt is sodium 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido)-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (syn isomer).

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, LI, DE, FR, GB, IT, NL, LU, SE

1. Wasserlösliche antibiotische Zusammensetzung, die Kristalle einer Cephemverbindung der folgenden Formel:



worin R^1 ein aliphatischer Kohlenwasserstoffrest ist, der geeignete(n) Substituent(en) aufweisen kann,

und R^2 (C_1-C_6)Alkyl ist, das mit einer 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Gruppe, die ein quaternäres Stickstoffatom enthält, substituiert ist, die eine Carbamoylgruppe an dem 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Ring aufweisen kann, oder ein Säureadditionssalz davon und ein pharmazeutisch verträgliches Kohlensäuresalz umfaßt.

2. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 1, worin die Cephemverbindung in Form ihres Säureadditionssalzes vorliegt.

3. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 2, worin das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Kohlensäuresalz 1:0,5 bis 1:4 Äquivalente beträgt.

4. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 3, worin das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Kohlensäuresalz 1:1 bis 1:3 Äquivalente beträgt.

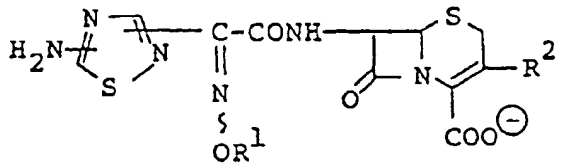
5. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 4, worin R^1 (C_1-C_6)Alkyl oder (C_2-C_6)-Alkenyl ist, R^2 1-Pyridiniomethyl ist und das pharmazeutisch verträgliche Kohlensäuresalz Alkalimetallhydrogencarbonat oder Alkalimetallcarbonat ist.

6. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 5, worin R^1 Allyl oder Propyl ist.

7. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 6, worin das Säureadditionssalz der Cephemverbindung 7-[2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylat-Hydrochlorid (Syn-Isomer) oder sein Dihydrat ist.

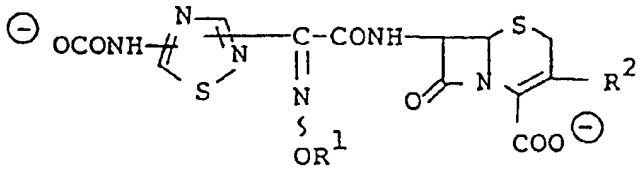
8. Wasserlösliche antibiotische Zusammensetzung nach Anspruch 7, worin das Alkalimetallhydrogencarbonat Natriumhydrogencarbonat ist, und das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Natriumhydrogencarbonat 1:1 äquivalent ist.

9. Verfahren zur Herstellung einer wasserlöslichen antibiotischen Zusammensetzung, welches das Zusammenmischen von Kristallen der Cephemverbindung der folgenden Formel:



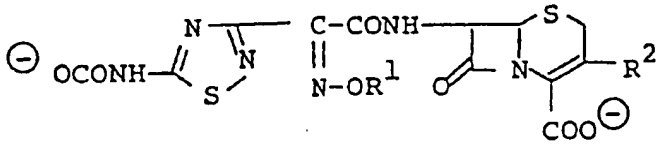
worin R^1 und R^2 jeweils wie im Anspruch 1 definiert sind, oder eines Säureadditionssalzes davon und einem pharmazeutisch verträglichen Kohlensäuresalz umfaßt.

10. Salz, welches Kation(en) und Anion der folgenden Formel umfaßt:

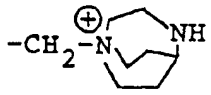


worin R^1 ein aliphatischer Kohlenwasserstoffrest ist, der geeignete(n) Substituent(en) aufweisen kann, und R^2 (C_1-C_6)Alkyl ist, das mit einer 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Gruppe, die ein quaternäres Stickstoffatom enthält, substituiert ist, die eine Carbamoylgruppe an dem 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Ring aufweisen kann.

11. Salz nach Anspruch 10, worin das Anion durch die folgende Formel dargestellt wird:



worin R^1 (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, und R^2 1-Pyridiniomethyl, Chinuclidiniomethyl oder eine Gruppe der Formel:



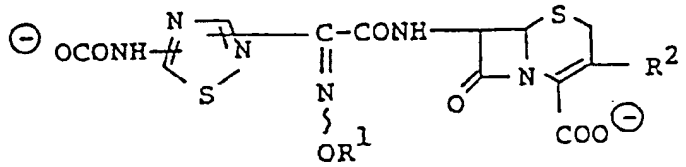
ist, wovon jede mit Carbamoyl substituiert sein kann.

12. Salz nach Anspruch 11, worin R^2 1-Pyridiniomethyl und das Kation ein Alkalimetall ist.

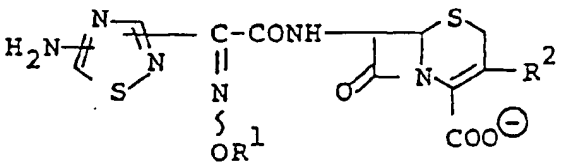
13. Salz nach Anspruch 12, das Natrium 7-[2-Allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylat (Syn-Isomer) ist.

14. Salz nach Anspruch 12, das Natrium 7-[2-(5-Carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylat (Syn-Isomer) ist.

15. Verfahren zur Herstellung eines Salzes, das Kation(en) und Anion umfaßt, der Formel:



worin R^1 ein aliphatischer Kohlenwasserstoffrest ist, der geeignete(n) Substituent(en) aufweisen kann, und R^2 (C_1-C_6)Alkyl ist, das mit einer 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Gruppe, die ein quaternäres Stickstoffatom enthält, substituiert ist, die eine Carbamoylgruppe an dem 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Ring aufweisen kann, welches das Reagieren einer Cephemverbindung der Formel:



worin R^1 und R^2 jeweils wie oben definiert sind, oder eines Salzes davon mit Kohlendioxyd in Gegenwart einer Base oder mit einem Kohlensäuresalz umfaßt.

16. Pharmazeutische Zusammensetzung, die ein Salz nach Anspruch 10 in Assoziation mit einem pharmazeutisch verträglichen, im wesentlichen nicht giftigen, Träger oder Exzipienten umfaßt.

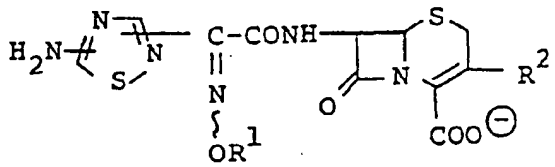
17. Verwendung eines Salzes nach Anspruch 10 zur Herstellung eines Medikaments für die Behandlung oder Prävention infektiöser Krankheiten.

18. Salz nach Anspruch 10 zur Verwendung als Medikament.

19. Salz nach Anspruch 10 zur Verwendung in der Behandlung oder Prävention infektiöser Krankheiten.

Patentansprüche für folgende Vertragsstaaten: ES, GR

1. Verfahren zur Herstellung einer wasserlöslichen antibiotischen Zusammensetzung, die das Zusammenmischen von Kristallen der Cephemverbindung der folgenden Formel:



worin R^1 ein aliphatischer Kohlenwasserstoffrest ist, der geeignete(n) Substituent(en) aufweisen kann, und R^2 (C_1-C_6)Alkyl ist, das mit einer 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Gruppe, die ein quaternäres Stickstoffatom enthält, substituiert ist, die eine Carbamoylgruppe an dem 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Ring aufweisen kann, oder eines Säureadditionssalzes davon mit einem pharmazeutisch verträglichen Kohlensäuresalz umfaßt.

2. Verfahren nach Anspruch 1, worin die Cephemverbindung in Form ihres Säureadditionssalzes vorliegt.

3. Verfahren nach Anspruch 2, worin das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Kohlensäuresalz 1:0,5 bis 1:4 Äquivalente beträgt.

4. Verfahren nach Anspruch 3, worin das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Kohlensäuresalz 1:1 bis 1:3 Äquivalente beträgt.

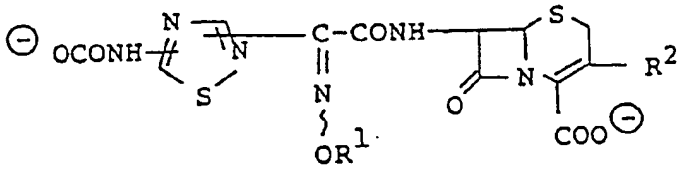
5. Verfahren nach Anspruch 4, worin R^1 (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, R^2 1-Pyridiniomethyl ist und das pharmazeutisch verträgliche Kohlensäuresalz Alkalimetallhydrogencarbonat oder Alkalimetallcarbonat ist.

6. Verfahren nach Anspruch 5, worin R^1 Allyl oder Propyl ist.

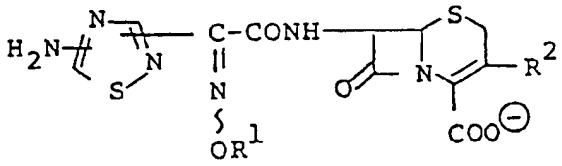
7. Verfahren nach Anspruch 6, worin das Säureadditionssalz der Cephemverbindung 7-[2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acetamido]-3-(1-pyridinio)methyl-3-cephem-4-car boxylat-Hydrochlorid (syn-Isomer) oder ihr Dihydrat ist.

8. Verfahren nach Anspruch 7, worin Alkalimetallhydrogencarbonat Natriumhydrogencarbonat ist und das Verhältnis des Säureadditionssalzes der Cephemverbindung zum Natriumhydrogencarbonat 1:1 äquivalent ist.

9. Verfahren zur Herstellung eines Salzes, das Kation(en) und Anion umfaßt, der Formel:

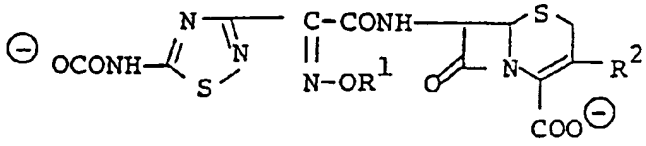


worin R^1 ein aliphatischer Kohlenwasserstoffrest ist, der geeignete(n) Substituent(en) aufweisen kann, und R^2 (C_1-C_6)Alkyl ist, das mit einer 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Gruppe, die ein quaternäres Stickstoffatom enthält, substituiert ist, die eine Carbamoylgruppe an dem 5- bis 10-gliedrigen mono- oder bicyclischen, heterocyclischen Ring aufweisen kann, welches das Reagieren einer Cephemverbindung der Formel:

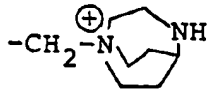


worin R^1 und R^2 jeweils wie oben definiert sind, oder eines Salzes davon mit Kohlendioxyd in Gegenwart einer Base oder mit einem Kohlensäuresalz umfaßt.

10. Verfahren nach Anspruch 9, worin das Anion durch die folgende Formel dargestellt wird:



worin R^1 (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist und R^2 1-Pyridiniomethyl, Chinuclidiniomethyl oder eine Gruppe der Formel:



ist, wovon jede mit Carbamoyl substituiert sein kann.

11. Verfahren nach Anspruch 10, worin R^2 1-Pyridiniomethyl ist und das Kation ein Alkalimetall ist.

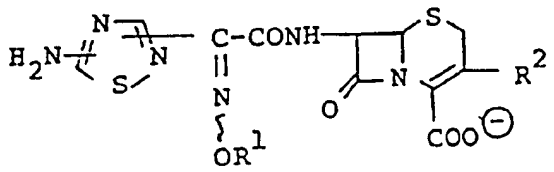
12. Verfahren nach Anspruch 11, worin das Salz Natrium 7-[2-Allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylat (Syn-Isomer) ist.

13. Verfahren nach Anspruch 11, worin das Salz Natrium 7-[2-(5-Carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacetamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylat (Syn-Isomer) ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, FR, GB, IT, NL, LU, SE,

1. Composition antibiotique soluble dans l'eau qui comprend des cristaux d'un céphème de la formule suivante :



dans laquelle R^1 est un radical d'un hydrocarbure aliphatique qui peut avoir un ou, plusieurs substituants appropriés et
R^2 est un groupe alkyle en C_1-C_6 substitué par un groupe hétérocyclique mono- ou bicyclique à 5 à 10 maillons contenant un atome d'azote quaternaire, qui peut avoir un groupe carbamoyle sur le cycle hétérocyclique mono ou bicyclique à 5 à 10 maillons
ou un de ses sels d'addition aux acides, et un sel d'acide carbonique pharmaceutiquement acceptable.

2. Composition antibiotique soluble dans l'eau selon la revendication 1, dans laquelle le céphème est sous la forme du sel d'addition aux acides.

3. Composition antibiotique soluble dans l'eau selon la revendication 2, dans laquelle le rapport du sel d'addition aux acides du céphème au sel d'acide carbonique est de 1:0,5 à 1:4 équivalents.

4. Composition antibiotique soluble dans l'eau selon la revendication 3, dans laquelle le rapport du sel d'addition aux acides du céphème au sel d'acide carbonique est de 1:1 à 1:3 équivalents.

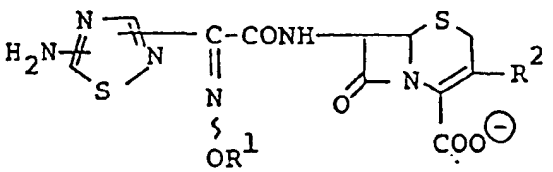
5. Composition antibiotique soluble dans l'eau selon la revendication 4, dans laquelle R^1 est un groupe alkyle en C_1-C_6 ou alcényle en C_2-C_6, R^2 est un groupe 1-pyridiniométhyle, et le sel d'acide carbonique pharmaceutiquement acceptable est un hydrogénocarbonate de métal alcalin ou un carbonate de métal alcalin.

6. Composition antibiotique soluble dans l'eau selon la revendication 5, dans laquelle R^1 est un groupe allyle ou propyle.

7. Composition antibiotique soluble dans l'eau selon la revendication 6, dans laquelle le sel d'addition aux acides du céphème est le 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acétamido]-3-(1-pyridinio)-méthyl-3-céphème-4-carboxylate chlorydrate (isomère syn) ou son dihydrate.

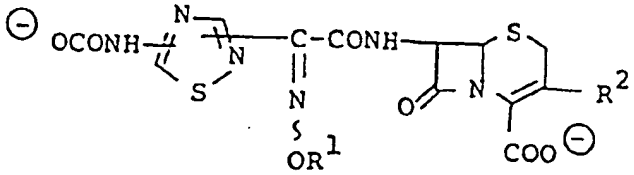
8. Composition antibiotique soluble dans l'eau selon la revendication 7, dans laquelle l'hydrogénocarbonate de métal alcalin est l'hydrogénocarbonate de sodium, et le rapport du sel d'addition aux acides du céphème à l'hydrogénocarbonate de sodium est de 1:1 équivalent.

9. Procédé de préparation d'une composition antibiotique soluble dans l'eau, qui comprend le fait de mélanger des crystaux du céphème répondant à la formule suivante :



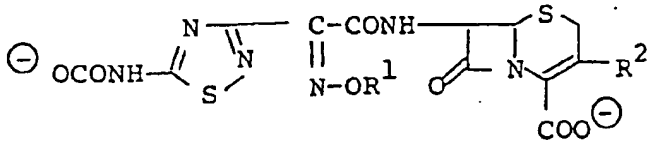
dans laquelle R^1 et R^2 sont chacun tels que définis dans la revendication 1, où un de ses sels d'addtion aux acides, et un sel d'acide carbonique pharmaceutiquement acceptable.

10. Sel comprenant un ou plusieurs cations et un anion de la formule :

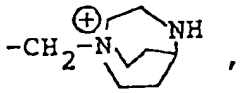


dans laquelle R^1 est un radical d'un hydrocarbure aliphatique qui peut avoir un ou plusieurs substituants appropriés, R^2 est un groupe alkyle en C_1-C_6 substitué par un groupe héthérocyclique mono- ou bicyclique à 5 à 10 maillons contenant un atome d'azote quaternaire, qui peut avoir un groupe carbamoyle sur le cycle hétérocyclique mono- ou bicyclique à 5 à 10 maillons.

11. Sel selon la revendication 10, dans lequel l'anion est représenté par la formule suivante :



dans laquelle R^1 est un groupe alkyle en C_1-C_6 ou alcényle en C_2-C_6 et R^2 est un groupe 1-pyridiniométhyle, quinuclidiniométhyle, ou un groupe de la formule :



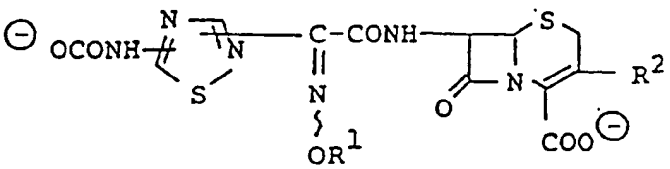
chacun d'eux pouvant être substitué par un groupe carbamoyle.

12. Sel selon la revendication 11, dans lequel R^2 est un groupe 1-pyridiniométhyle, et le cation est un métal alcalin.

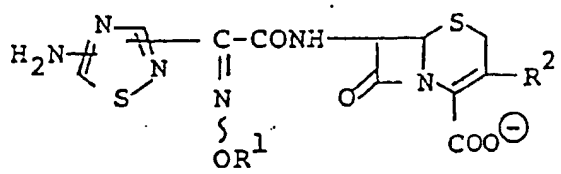
13. Sel selon la revendication 12, qui est le 7-[2-allyloxyimino-2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-acétamido]-3-[1-pyridinio)méthyl-3-céphème-4-carboxylate de sodium (isomère syn).

14. Sel selon la revendication 12, qui est le 7-[2-(5-carboxylatoamino-1,2,4-thiadiazol-3-yl)-2-propyloxyiminoacétamido-3-(1-pyridinio)méthyl-3-céphème-4carboxylate de sodium (isomère syn).

15. Procédé de préparation d'un sel comprenant un ou plusieurs cations et un anion de la formule :



dans laquelle R^1 est un radical d'un hydrocarbure aliphatique qui peut avoir un ou plusieurs substituants appropriés, R^2 est un groupe alkyle en C_1-C_5 substitué par un groupe hétérocyclique mono- ou bicyclique à 5 à 10 maillons contenant un tome d'azote quaternaire qui peut avoir un groupe carbamoyle sur le cycle hétérocyclique mono- ou bicyclique à 5 à 10 maillons,
qui comprend le fait de faire réagir un céphème de la formule :



dans laquelle R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels,
avec de l'anhydride carbonique en présence d'une base; ou avec un sel de l'acide carbonique.

16. Composition pharmaceutique comprenant un sel selon la revendications 10 en association avec un support ou excipient pratiquement non toxique, pharmaceutiquement acceptable.

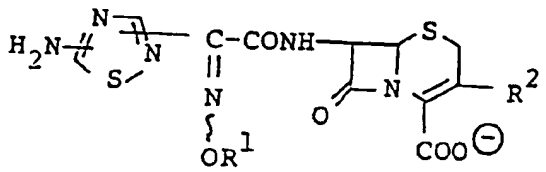
17. Utilisation d'un sel selon la revendication 10 pour la fabrication d'un médicament pour traiter ou prévenir les maladies infectieuses.

18. Sel selon la revendication 10 destiné à l'utilisation comme médicament.

19. Sel selon la revendication 10, pour l'utilisation dans le traitement ou la prévention des maladies infectieuses.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'une composition antibiotique soluble dans l'eau, qui comprend le fait de mélanger des cristaux du céphème de la formule suivante :



dans laquelle R^1 est un radical d'un hydrocarbure aliphatique qui peut avoir un ou plusieurs substituants appropriés et
R^2 est un groupe alkyle en C_1-C_6 substitué par un groupe hétérocyclique mono- ou bicyclique à 5 à 10 maillons contenant un atome d'azote quaternaire, qui peut avoir un groupe carbamoyle sur le cycle hétérocyclique mono- ou bicyclique à 5 à 10 maillons,
ou un de ses sels d'addition aux acides, et un sel d'acide carbonique pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel le céphème est sous la forme du sel d'addition aux acides.

3. Procédé selon la revendication 2, dans lequel le rapport du sel d'addition aux acides du céphème au sel d'acide carbonique est de 1:0,5 à 1:4 équivalents.

4. Procédé selon la revendication 3, dans lequel le rapport du sel d'addition aux acides du céphème au sel d'acide carbonique est de 1:1 à 1:3 équivalents.

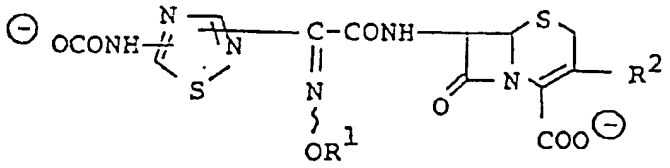
5. Procédé selon la revendication 4, dans lequel R^1 est un groupe alkyle en C_1-C_6 ou alcényle en C_2-C_6, R^2 est un groupe 1-pyridiniométhyle, et le sel d'acide carbonique pharmaceutiquement acceptable est un hydrogénocarbonate de métal alcalin ou un carbonate de métal alcalin.

6. Procédé selon la revendication 5, dans lequel R^1 est un groupe alcyle ou propyle.

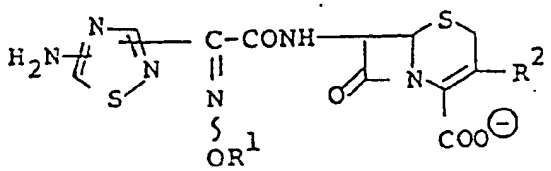
7. Procédé selon la revendication 6, dans lequel le sel d'addition aux acides du céphème est le 7-[2-allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)-acétamido]-3-(1-pyridinio)méthyl-3-céphème-4-carboxylate chlorydrate (isomère syn) ou son dihydrate.

8. Procédé selon la revendication 7, dans lequel l'hydrogénocarbonate de métal alcalin est l'hydrogénocarbonate de sodium, et le rapport du sel d'addition des acides du céphème à l'hydrogénocarbonate de sodium est de 1:1 équivalent.

9. Procédé pour préparer un sel comprenant un ou plusieurs cations et un anion de la formule :

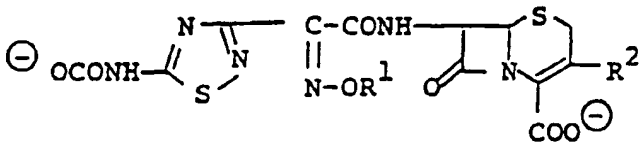


dans laquelle R^1 est un radical d'un hydrocarbure aliphatique qui peut avoir un ou plusieurs substituants appropriés,
R^2 est un groupe alkyle en C_1-C_6 substitué par un groupe hétérocyclique mono- ou bicyclique à 5 à 10 maillons contenant un atome d'azote quaternaire qui peut avoir un groupe carbamoyle sur le cycle hétérocyclique mono- ou bicyclique à 5 à 10 maillons
qui comprend le fait de faire réagir un céphème de la formule :



dans laquelle R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ces sels,
avec de l'anhyride carbonique en présence d'une base, ou avec un sel d'acide carbonique.

10. Procédé selon la revendication 9, dans lequel l'anion est représenté par la formule suivante :



dans laquelle R^1 est un groupe alkyle en C_1-C_6 ou alcényle en C_2-C_6 et R^2 est un groupe 1-pyridiniométhyle, quinuclidiniométhyle, ou un groupe répondant à la formule :